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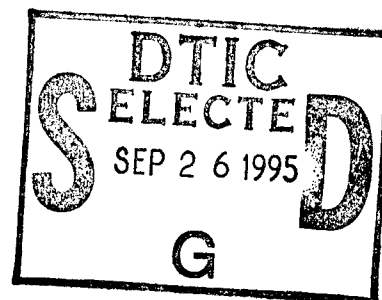
TITLE: Breast Cancer Predoctoral Training Program

PRINCIPAL INVESTIGATOR: Stuart A. Aaronson, M.D.

CONTRACTING ORGANIZATION: Mount Sinai School of Medicine
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13. ABSTRACT (Maximum 200 words) The new interdisciplinary predoctoral training program in breast cancer research was initiated with the award by the USAMDRC for four years support. This program provides rigorous training in a flexible, individualized predoctoral program. Three trainees (two PhD students and one MD/PhD student) were selected from the current pool of students who were starting their thesis research in an area relevant to breast cancer research. A variety of activities have been organized during this first-year of support which bring together on a regular basis faculty from clinical as well as basic science departments and trainees to present and discuss issues relevant to breast cancer. These include a new Breast Study Group, a new seminar series in Signal Transduction which supplements the Cancer Center seminars, and a new Molecular Oncology Research Colloquium. A new course in Cancer Biology for graduate students was taught by training program faculty. In addition, program faculty and trainees participated in new collaborations both in research and journal clubs. This program has served as an important stimulus to new and existing faculty to develop programs that will utilize a multidisciplinary approach to understand the molecular mechanisms important in breast cancer and to develop strategies to intervene effectively in the treatment of this disease.				
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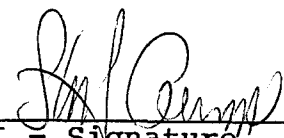

PI - Signature 7/27/95
Date

Table of Contents

	Page No.
Front Cover	1
SF 298 - Report Documentation Page	2
Foreword	3
Table of Contents	4
Introduction	5
Body	5
Conclusions	10
References	11

Appendix Material

Appendix I - Cancer Course announcement and outline

Appendix II - Seminar Series announcements

Signal Transduction Seminar Series

The Derald H. Ruttenberg Cancer Center Special Seminars

Appendix III - Dr. Ravi Iyengar -- Biographical Sketch and Training Record

Appendix IV - Examples of Cancer Center Breast Study Group announcements

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Progress Report Summary

Year 1 (7/1/94 - 6/30/95)

Introduction:

The new interdisciplinary predoctoral training program in breast cancer research for predoctoral students was initiated with the award by the USAMDRC of \$400,000 for four years support. This program provides rigorous training in a flexible, individualized predoctoral program. Trainees are selected from the current pool of students (both PhD and MD/PhD students) who are already committed to pursuing their thesis research with one of the training program faculty members. Progress in implementation of the training program objectives for the first year of support (7/1/94 - 6/30/95), as outlined in the Statement of Work of the original grant proposal, will be described.

Body:

Selection of trainees: The budget for the first year provided partial stipend and tuition support for three trainees. Training program faculty members were asked to propose PhD or MD/PhD students for support by the training grant. The main criterion was that these students should be committed to pursuing research related to breast cancer. After reviewing the credentials of the proposed students and after consultation with selected members of the Steering Committee, three trainees were selected by the Program Director. Their academic background and research projects are summarized below.

Advisory Committees for trainees: Each trainee had an appointed Advisory Committee which met with the trainee at least twice during the past year. At these meetings, the trainees summarized their educational activities (courses, journal clubs, seminars) and briefly reviewed the progress in their research.

Cancer Course for trainees: A new course in Cancer Biology was organized by training program faculty (Drs. Aaronson, Chan, Johnson, Licht, Manfredi, Kohtz). This course was offered in the Spring 1995 semester to all interested students in the graduate program and was specifically recommended to breast cancer trainees. The course was taught in three five-week modules, focusing on oncogenes (module 1), tumor suppressor genes (module 2) and tumor biology (module 3). An outline of the course is provided in Appendix I. Active participation by the students was required. The course focused on presentation of current journal articles by the students and each module was accompanied by a long written assignment at the end of each module. These written assignments took the form of either a take-home exam, a review of the literature, or a grant proposal.

Ten students signed up for the course. Judging from the course evaluations provided by the students, they felt that the course was well-organized and covered new material that they had not previously been exposed to in other courses. This course will continue to be given on an annual basis.

Journal Club for trainees: A weekly journal club which focused on tumor suppressors and the cell cycle was organized by Drs. Robert Krauss and James Manfredi. This journal club provided an informal setting for interested trainees, postdoctoral fellows, and faculty to present and critically review recent journal articles related to tumor suppressors.

Seminars/Colloquia/Conferences: A new Signal Transduction seminar series, open to the Mount Sinai School of Medicine community and advertised widely on campus, was organized by Drs. Lu-Hai Wang and Ravi Iyengar. This seminar series focused on various aspects of signal transduction. A summary of speakers is appended (Appendix II).

The Derald H. Ruttenberg Cancer Center, under the leadership of Dr. Stuart Aaronson, also organized a number of special seminars (see Appendix II). These seminars were advertised on campus and were open to the entire Mount Sinai community. Often these seminars were given by investigators who were being recruited for faculty positions in the Cancer Center. Some of these investigators will join, or have joined, the faculty and will be added to this training program as training faculty at the appropriate time.

In addition, a new Molecular Oncology Research Colloquium was organized by Dr. Lu-Hai Wang. Once a month, a member from each of two laboratories involved in cancer research presented a short update of their research findings. These colloquia were attended by trainees, postdoctoral fellows, and faculty and stimulated discussions and interactions between program faculty.

The combined Surgery, Pathology, Radiology, Radiation Oncology and Medical Oncology Breast Conference continued to be held monthly. At these interdepartmental conferences clinicians reviewed of five or six clinical cases at each meeting and discussed relevant issues related to breast cancer treatment at Mount Sinai Hospital. These conferences were particularly useful for the PhD trainees who normally do not get much exposure to the clinical aspects of breast cancer.

Recruitment of additional faculty: In the past year, Dr. Ravi Iyengar has joined the training faculty. A short biographical sketch and a summary of his training record is appended (Appendix III). Dr. Iyengar is Professor of Pharmacology and is on the doctoral faculty of the Molecular Biology subarea. Before coming to Mount Sinai in 1986, he was on the faculty of the Cell Biology Department at Baylor College of Medicine. He is well-known and highly respected in the field of signal transduction mediated by heterotrimeric G proteins. His research uses biochemical and molecular biological techniques to elucidate the molecular mechanisms involved in signal transduction. He has trained 4 predoctoral students and 6 postdoctoral fellows since he has been at Mount Sinai. Currently his research group comprises 5 students and 3 postdoctoral fellows.

As the Cancer Center continues to recruit additional faculty, it is anticipated that in the coming year, several faculty will join this predoctoral training program. Faculty newly recruited to other departments are also likely to be appropriate mentors for trainees. It is anticipated that the seminars, journal clubs, and research colloquia that have been organized during the past year will help to advertise this training program to these new faculty and will stimulate research collaborations in the field of breast cancer.

Collaborations between program faculty: In an attempt to foster collaborations between program faculty, the Cancer Center Breast Study Group was organized by Drs. Aaronson and Brower. This group, which consisted of all training program faculty, met several times during the year. At each meeting, one or more program faculty presented their research program in an informal setting which encouraged discussion. Faculty who have presented their research to this group include Drs. Edward Johnson, Dr. Raphael Miral y Lopez, Dr. Paolo Fedi, and Dr. Carol Bodian. An example of announcements of this group meeting is appended (Appendix IV). The next meeting, scheduled for July 27, 1995, will feature brief reports from each of the three trainees supported by this training grant and will give the trainees an opportunity to present their research findings in a public forum.

A joint research meeting between the laboratories of Drs. Robert Krauss of the Department of Biochemistry and James Manfredi of the Department of Medicine has been established and meets on a regular basis. Other new collaborations between program faculty that have come into being during the past year and have already been mentioned are the Signal Transduction Seminar Series, organized by Drs. Iyengar and Wang, the Molecular Oncology Research Colloquia, organized by Dr. Wang, and the Cancer Course, organized by Drs. Aaronson, Chan, Johnson, Licht, Manfredi, and Kohtz.

Trainees:

The following predoctoral trainees were supported by this training grant during the past project period, 7/1/94-6/31/95. All trainees were appointed on 7/1/94 for one year and will continue to be supported during the next project period, 7/1/95-6/31/96.

Ulrich Hermanto

MD/PhD Program, Year 3
Thesis Advisor: Lu-Hai Wang, Ph.D.

B.A. (Chem./Biol.) 1992 Boston University

Max Fonarev

PhD Program, Year 2
Thesis Advisor: James Manfredi, Ph.D.

B.S. (Physics) 1992 Moscow Institute of Physics and Technology, USSR
M.S. (Molec. Biol.) 1993 Moscow Institute of Physics and Technology, USSR

Tara Ann Santore

PhD Program, Year 3
Thesis Advisor: Ravi Iyengar, Ph.D.

B.S. (Biology) 1990 St. Francis College, Brooklyn, NY
M.S. (Molec. Biol.) 1992 Long Island University, NY

Trainee Research Projects:

Ulrich Hermanto is working on a project that involves the study of intracellular signal transduction in breast cancer cells. The first objective is to identify breast carcinoma cell lines which display signaling abnormalities when compared to normal or other breast cancer cell lines. Biochemical analyses of protein expression by Western blotting and in vitro kinase assays have been performed on normal cell lines (MCF-10 and AB589) and a variety of breast cancer cell lines (SK-BR3, MCF-7, T47-D, BT20, BT474, BT483, MDA-MB-231, Hs578t, and ZR-75-1).

As transformation usually results in increased phosphorylation of certain substrates on tyrosine residues, the phosphoprotein pattern of these cell lines was analyzed by IP/western using anti P-Tyr antibodies (Abs). Immunoblots showed phosphorylated proteins of MW 180-200 kDa and 100-120 kDa. Receptor protein tyrosine kinases (RPTKs) were determined to be candidates for some of these phosphoproteins and

subsequently, expression analysis of various receptors was performed by using anti-EGFR Ab, anti-ErbB2 Ab, anti-Insulin Receptor (IR) Ab, anti-Insulin-like growth factor1 Receptor (IGFR) Ab in IP/western and IP/anti P-Tyr western. Receptor kinase activity was assessed by in vitro autokinase assays. Elevated EGFR expression was detected in one cell line. All cell lines expressed ErbB2; however, 3 cell lines displayed modest to very high levels of expression. One cell line overexpressed IR. While all cell lines expressed IGFR to some degree, 50% of the breast cancer cell lines overexpressed the receptor as compared to normal, and kinase activity (unstimulated or in serum) correlated with the level of receptor expression.

Protein expression and phosphorylation of other signaling proteins was also analyzed by IP/western. p46 and p52 SHC protein expression levels were uniform across all cell lines. However, several cancer cell lines did not express p62 SHC to levels comparable to those of the normal cell lines and SHC phosphorylation in cells grown in serum correlates with expression levels. PLC-gamma expression was uniform but activity as assessed by PLC-gamma phosphorylation was elevated in two breast cancer cell lines. IRS-1 protein expression was highly elevated in two breast cancer cell lines. SOS protein expression was elevated in one breast cancer cell line. Constitutive MAP kinase activity under serum-free, unstimulated conditions was observed in at least one breast carcinoma line.

From these initial screening experiments, it is clear that most of the breast cancer cell lines studied thus far exhibit some sort of aberrant expression profile in regard to molecules involved in normal signaling. The role of such abnormalities in the transformed phenotype of these cells is unclear but can be better defined by the introduction of dominant negative mutants of the protein(s) in question. The next part of this project involves the transfection of expression plasmids of various dominant negative mutants like GRB2, H-ras, IGFR, and SHC into the candidate cell lines. Since these mutants may be toxic to normal growth, expression can be regulated by the tetracycline-transactivator (tTA) expression system established by Bujard et al. Following induced expression of the mutant protein, phenotypic changes in these cells will be assessed by growth rate (^3H thymidine incorporation in liquid culture), anchorage independence (colony formation in soft agar), and in vivo tumorigenesis (tumor induction in mice).

Max Fonarev is working in Dr. James Manfredi's lab on a project involving the regulation of the tumor suppressor activity of p53 by cyclin-dependent kinases. Specifically, he is studying the underlying mechanism by which overexpression of two cyclins, cyclin E and cyclin D1, contributes to the oncogenic process in human breast cancer. The tumor suppressor protein p53 is phosphorylated by cyclin-dependent kinases and transcriptionally activates the gene encoding for a cyclin-dependent kinase inhibitor, p21. The hypothesis to be tested in this project is whether cyclin overexpression exerts its oncogenic effects via inactivation of the tumor suppressor activity of p53, either by directly modifying the p53 by phosphorylation or by blocking the effects of its downstream target p21.

The initial approach has been to establish breast carcinoma cell lines which overexpress the various cyclins. He found that sustained cyclin overexpression was cytotoxic to this cell line. Therefore, he is now attempting to examine the effects of the overexpression of various cyclins in a transient assay system rather than in established clones. Two breast carcinoma cell lines are being used for these studies. MCF7 cells, after transient transfection with plasmids that express cyclins A, B1, B2, D1, D3 or E will be subjected to DNA damage and then examined for their ability to respond with a p53-

dependent G1 phase arrest. Co-transfection with a plasmid expressing the cell surface antigen CD20 will allow subsequent staining with a fluorescently tagged anti-CD20 antibody to distinguish transfected from untransfected cells by flow cytometry. MDA-MB-433 cells, which are null for p53 expression, will be co-transfected with the cyclin plasmids and a plasmid which overexpresses wild-type p53. Due to a high co-transfection efficiency, only those cells which receive a cyclin plasmid will be expressing p53 and thus effects of cyclin overexpression of p53 function will be more readily detected. In such a system, both the ability of p53 to bind to DNA by electrophoretic mobility shift assays and the ability to activate transcription by cotransfection with suitable reporter plasmids can be tested.

In collaboration with Dr. Stave Kohtz in the Department of Pathology, Mr. Fonarev has been analyzing clones of C2C122 cells which overexpress cyclin D1. Preliminary studies suggest that overexpression of cyclin D1 in these cells blocks the G1 phase arrest in response to DNA damage. Although p53 levels increase in the cyclin D1 overexpressing cells after DNA damage, DNA binding of this p53 is poor suggesting that overexpression of cyclin D1 may directly affect the ability of p53 to interact with its target sequences. These results are currently being confirmed and will be correlated with the results to be obtained in the breast carcinoma cell lines.

Mechanisms for regulating p53 may reflect mechanisms of oncogenesis. By inhibiting the ability of the DNA damage signal to be translated into either growth arrest or apoptosis, cells can sustain genetic lesions which can be propagated and result in oncogenic progression. Given the role of overexpression of different cyclins in human breast cancer, the research outlined here can serve as the basis for future clinical studies in both the prognosis and treatment of human breast carcinomas. Thus, elucidating a mechanism for regulation of wild-type p53 by cyclin proteins represents an important avenue in breast cancer research.

Tara Santore is pursuing research in the laboratory of Dr. Ravi Iyengar, who has recently been added to this predoctoral training program as a preceptor. The overall goal of her thesis research project is to determine if interactions between signaling pathways can be used to suppress expression of the transformed phenotype in mammary epithelial cells.

It has been known for some time that activation of growth factor receptor-mediated signaling pathways results in transformation. Activated Ras is found in more than 25% of human tumors. Previous results from Dr. Iyengar's lab had shown that interactions between the cAMP and MAP-kinase pathways can be used to suppress transformation. Expression of activated G_{α_s} only modestly increases the cellular concentrations of cAMP, but almost completely suppressed transformation of NIH-3T3 cells by H-Ras. Since blockade of transformation by G_{α_s} could be achieved without raising cellular cAMP concentrations to harmful levels it was thought that targeted implantation of the activated G_{α_s} may be a useful strategy for preventing the development of cancer in some tissues.

Since mammary carcinomas appear to have alterations in tyrosine kinase signaling pathways it is possible that one of the causes for the transformation is enhanced signaling through the MAP-kinase pathway. Signaling through the MAP-kinase pathway can be inhibited by G_{α_s} -mediated activation of PKA. Thus, it may be possible to suppress transformation and expression of the transformed phenotype in vivo by expression of activated G_{α_s} in mammary epithelial cells. To test if expression of activated G_{α_s} will suppress mammary tumorigenesis in vivo Ms. Santore has begun construction of an adenovirus vector containing the mutant G_{α_s} tagged with the FLAG epitope.

Adenovirus is a good choice as an expression system for gene therapy in mammalian systems. Firstly, its DNA genome of 36,000 base pairs can be manipulated by recombinant DNA techniques. Second the genome does not undergo rearrangement at a high rate. Third, the viral particle is fairly stable. Lastly, the virus replicates in permissive cells very efficiently enabling high titer viral stocks to be produced.

Two plasmids have been obtained from Dr. F.L. Graham's laboratory. Plasmid pJM17 encodes for the entire adenovirus genome, with a pBR322 insertion in the E1 gene. Because insertion of this plasmid DNA causes the genome to exceed the packaging constraints of the adenovirus, production of viral progeny can only occur by internal rearrangement (a rare event) or by recombination of pJM17 with a shuttle plasmid (pCA14) containing a foreign gene. In addition, because the E1 gene is required for proper viral packaging, 293 cells, which have been transformed and constitutively express the E1 gene products E1a and E1b, are used in these experiments to produce infectious, but recombinant deficient, progeny virus.

The shuttle plasmid pCA14-F α s* was constructed by inserting the G α s* cDNA with the FLAG epitope at its 5' end. pCA14-F α s* and pJM17 were then co-transfected into 293 cells. After cotransfection, recombination can occur between the shuttle vector containing the FLAG tagged G α s* and the adenovirus genome. Currently transfections into 293 cells have been carried out and plaques have been isolated. The clones isolated from these plaques are being assayed to ensure that proper recombination has occurred.

Once the recombinant adenoviruses containing mutant G α s are obtained, Ms. Santore will test in vitro if the expression of activated G α s will result in suppression of colony formation in soft agar by several human breast cancer cell lines, including MCF-7, MDZA-231 and MDA453. She will also generate tumors in Nu/Nu mice by injection of these cell lines and determine if application of the recombinant adenovirus containing G α s results in suppression of these tumors.

Trainee Travel:

Ulrich Hermanto attended the 11th Annual Oncogene Meeting which was held in June, 1995, in Frederick, Maryland. In August, 1994, Max Fonarev attended a conference on DNA Tumor Viruses held at Cold Spring Harbor Laboratories. This meeting devoted several sessions on tumor suppressor proteins and their role in cancer, a subject closely related to his research.

Conclusions:

The various Seminars, Courses, Colloquia that have been organized during the past year will likely continue to stimulate interest among the faculty and students in a multidisciplinary approach to the study of breast cancer. It is likely that some of these activities will be expanded to meet more frequently and to include more faculty. As new faculty are recruited to the Cancer Center and to other departments in the School of Medicine they will be made aware of these activities and will hopefully join the training program as training faculty. These activities will also serve to stimulate research collaborations among the Mount Sinai faculty in the area of breast cancer and will hopefully lead to new insights into the molecular mechanisms responsible for this disease.

The objectives for year 1 of the program have been met. These objectives will be expanded during year 2 of the training program, as listed in the Statement of Work of the original grant proposal.

The first year of this training program supported three trainees. During the next budget period, the number of trainees supported by this grant will be increased to a total of 5 trainees. Faculty have already been asked to submit the names of suitable candidates for the trainee slots. The Steering Committee will meet to choose the most qualified students for these slots and to assign Advisory Committees for these trainees. Each current trainee has submitted a written progress report and will give an oral presentation to the Cancer Center Breast Study Group. This will allow the faculty to review the progress of these trainees.

This training program has proved to be a highly successful, visible effort on campus to stimulate interest in research in breast cancer. The program has attracted the interest of existing faculty as well as new faculty recruited to both the Cancer Center and other departments on campus. New faculty have joined the program and it is anticipated that in the coming year several faculty will either actively join the program or enter into collaborative research and teaching efforts of the program faculty.

References:

No publications resulting from trainee research directly related to this training grant have yet appeared.

Topics in Cancer Biology

A new, modular course dealing with topics in cancer biology will be offered in the Spring 1995 semester. This course is intended for students who have completed Core Courses I and II or equivalent courses. The course material will focus on recent research findings in relevant areas of cancer biology and will be taught largely from primary literature reports.

Each 5-week module may be taken separately; however, the three modules are arranged to provide a comprehensive and cohesive study of oncogenes, tumor suppressor genes, and tumor biology. The course will consist of lectures, student presentations, and invited speakers. The course will meet twice a week (**Tuesdays and Thursdays, 1:30 - 3 PM**) starting Feb. 7, 1995. One credit will be given for satisfactory completion of each module.

I. Oncogenes -- organized by Drs. Ed Johnson and Andrew Chan

Feb. 7 - March 9

Topics include: viral oncogenes
oncogene activation/amplification
ras oncogenes
autocrine growth factors
chromosome translocations

II. Tumor Suppressor Genes -- organized by Drs. Jim Manfredi and Jonathan Licht

March 14 - April 13

Topics include: pRb (retinoblastoma protein)
p53
cyclin-dependent kinase inhibitors
WT1 (Wilms' tumor gene product)
colorectal tumorigenesis
mismatch repair genes
neurofibromatosis

III. Tumor Biology -- organized by Drs. Stave Kohtz and David Burstein

April 18 - May 18

Topics include: tumor classification and diagnosis
tumor progression
apoptosis
metastasis/angiogenesis
immune surveillance
viral carcinogens
cancer therapy

Oncogenes -- E. Johnson and A. Chan

Feb. 7	Tu	Oncogenes defined
Feb. 9	Th	Journal discussion
Feb. 14	Tu	Oncogene activation/amplification
Feb. 16	Th	Journal discussion
Feb. 21	Tu	<i>Ras</i> oncogenes
Feb. 23	Th	Journal discussion
Feb. 28	Tu	Autocrine growth factors
March 2	Th	Journal discussion
March 7	Tu	Chromosome translocation
March 9	Th	Journal discussion

Tumor Suppressor Genes -- J. Manfredi and J. Licht

March 14	Tu	Introduction
March 16	Th	pRb
March 21	Tu	pRb
March 23	Th	p53
March 28	Tu	p53
March 30	Th	Cyclin-dependent kinase inhibitors
April 4	Tu	WT1
April 6	Th	Colorectal tumorigenesis
April 11	Tu	Mismatch repair genes
April 13	Th	Neurofibromatosis

Tumor Biology -- S. Kohtz and D. Burstein

April 18	Tu	Tumor classification/diagnosis/transformed cells
April 20	Th	Apoptosis/Metastasis/Angiogenesis
April 25	Tu	"
April 27	Th	Discussion
May 2	Tu	Immune surveillance
May 4	Th	Discussion
May 9	Tu	Viral carcinogens
May 11	Th	Discussion
May 16	Tu	Cancer therapy
May 18	Th	Discussion

Signal Transduction Seminar Series

Winter-Spring 1995

January 27, 1995	Joan Massague, Ph.D. Memorial Sloan-Kettering Cancer Center "Origin and Targets of Antiproliferative Signals"
May 5, 1995	Morris White, Ph.D. Joslin Diabetes Center and Harvard Medical School "IRS-Signaling Proteins: Coming into Phase for Insulin and Cytokine Signaling"
May 12, 1995	Beverly Errede, Ph.D. University of North Carolina "Dynamics and Organization of MAP-Kinase Activation"
June 23, 1995	Richard Scheller, Ph.D. Stanford University, Howard Hughes Medical Institute "Molecular Mechanism of Synaptic Transmission"
June 30, 1995	J. Silvio Gutkind, Ph.D. NIDR-NIH "Small GTP Binding Proteins of the Ras-Rho Family Control Divergent MAP-Kinase Cascades: A role in Signaling from the Cell Surface to the Nucleus"

PLEASE POST

**THE DERRALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

"pRb Deficiency, Cell Cycle Control and Apoptosis"

ALEXANDRU ALMASAN, PH.D.
DEPARTMENT OF MOLECULAR BIOLOGY & VIROLOGY
GENE EXPRESSION LABORATORY
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
LA JOLLA, CA

WEDNESDAY, AUGUST 24, 1994

12:00 - 1:00 PM

ANNENBERG 25-51

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

11/3/94

**THE DERALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

**"Chemical Dynamics of the Camptothecin Anticancer Drugs
in Human Blood"**

THOMAS G. BURKE, PH.D.
ASSISTANT PROFESSOR
COLLEGE OF PHARMACY
THE OHIO STATE UNIVERSITY
DIVISION OF PHARMACEUTICS
AND PHARMACEUTICAL CHEMISTRY

THURSDAY, NOVEMBER 17, 1994
12:00 - 1:00 PM
ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

THE DERALD H. RUTTENBERG CANCER CENTER SPECIAL SEMINAR

"Transcription Factors and Ras Transformation"

MICHAEL A. TAINSKY, PH.D.
ASSOCIATE PROFESSOR
DEPARTMENT OF TUMOR BIOLOGY
THE UNIVERSITY OF TEXAS
M.D. ANDERSON CANCER CENTER
HOUSTON, TX

MONDAY, DECEMBER 19, 1994

12:00 - 1:00 PM

ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

(Revised 12/20/94)

PLEASE POST

THE DERALD H. RUTTENBERG CANCER CENTER SPECIAL SEMINAR

"Enzymatic Analysis of the DNA Synthesis Machinery
in Humans - Implications for Cancer Biology"

ZHEN-QIANG PAN, PH.D.
NUCLEIC ACIDS BIOCHEMISTRY/SYNTHESIS
MOLECULAR BIOLOGY PROGRAM
MEMORIAL SLOAN-KETTERING CANCER CENTER

THURSDAY, DECEMBER 22, 1994

3:30 - 4:45 PM

ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

1/24/95

**THE DERALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

"Cell Cycle Regulation During Development"

JEAN GAUTIER, PH.D.
ASSOCIATE MEMBER
ROCHE INSTITUTE OF MOLECULAR BIOLOGY
NUTLEY, NJ

TUESDAY, JANUARY 31, 1995

4:00 - 5:00 PM

ANNENBERG 25-51

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

1/24/95

**THE DERALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

**"The Recombination Activating Genes Rag-1 and Rag-2:
Lymphoid Development in the Absence of Rag-1"**

EUGENIA SPANOPOULOU, PH.D.
WHITEHEAD INSTITUTE
ROCKEFELLER UNIVERSITY
NEW YORK, NY

THURSDAY, FEBRUARY 2, 1995

3:45 - 4:45 PM

ANNENBERG 25-51

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

1/24/95

**THE DERALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

**"Identification of Tumor Suppressor Genes
by Monochromosome Transfer"**

BERNARD WEISSMAN, PH.D.
LINEBERGER CANCER RESEARCH CENTER
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC

MONDAY, FEBRUARY 6, 1995

11:00 A.M. - 12:00 NOON

ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

3/7/95

**THE DERALD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

"Molecular Analysis of Vascular Endothelial
Cell Development and Differentiation"

THOMAS SATO, PH.D.
ROCHE INSTITUTE OF MOLECULAR BIOLOGY
NUTLEY, NJ

MONDAY, MARCH 27, 1995

3:00 - 4:00 PM

ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

PLEASE POST

5/10/95

**THE DERAULD H. RUTTENBERG CANCER CENTER
SPECIAL SEMINAR**

**"Molecular Mechanisms of Endothelial
Cell Growth and Differentiation"**

WERNER RISAU, PH.D.
DIRECTOR
MAX-PLANCK-INSTITUT FUR PHYSIOLOGISCHE
UND KLINISCHE FORSCHUNG
W.G. KERCKHOFF-INSTITUT
ABTEILUNG MOLEKULARE ZELLBIOLOGIE
BAD NAUHEIM, GERMANY

WEDNESDAY, MAY 17, 1995

12:00 - 1:00 PM

ANNENBERG 18-85

HOST: STUART A. AARONSON, M.D. (X46470)

CURRICULUM VITAE

RAVI IYENGAR

ACADEMIC TRAINING:

1971	B.S. in Chemistry/Physics, Bombay University, Bombay, India
1973	M.S. in Biophysics, Bombay University, Bombay, India
1975	M.S. in Biophysical Sciences, University of Houston, Houston
1977	Ph.D. in Biophysical Sciences, University of Houston, Houston

POSTDOCTORAL TRAINING:

1977-1980	Department of Cell Biology (Laboratory of Dr. L. Birnbaumer), Baylor College of Medicine
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PROFESSIONAL EXPERIENCE:

1973-1974	Scientific Officer Trainee, Department of Atomic Energy; Government of India, Bombay, India
1980-1985	Assistant Professor, Department of Cell Biology, Baylor College of Medicine, Houston
1985-1986	Associate Professor, Department of Cell Biology, Baylor College of Medicine, Houston
1986-1990	Associate Professor, Department of Pharmacology, Mount Sinai School of Medicine, New York
1990-present	Associate Professor, Department of Pharmacology, Mount Sinai School of Medicine, New York

AWARDS:

1978-1980	National Research Service Award, NIH
1980-1983	New Investigator Award, NIH
1983-1988	Established Investigator Award, American Heart Association

SCIENTIFIC SERVICE:

1990-1996	Member, Editorial Board, Journal of Biological Chemistry
1988-1991	Member, Editorial Board, Endocrinology
1983-1987	Member, Editorial Board, Molecular and Cellular Endocrinology
1988-1989, 1991-1995	Member, Fellowship Review Committee, American Heart Association
1989-1992	Member Cellular Physiology and Pharmacology Research Study Committee, American Heart Association
1995-1999	Member, Pharmacology Study Section, NIH

PUBLICATIONS (total of 58 primary publications and 50 reviews and book chapters):

Somkuti, S.A., Hildebrandt, J.D., Herberg, J.T., and Iyengar, R. (1982) Divalent cation regulation of adenylyl cyclases: an allosteric site on the catalytic component. *J. Biol. Chem.* 257: 6387-6393.

Hildebrandt, J., Sekura, R.D., Codina, J., Iyengar, R., Manclark, C.R. and Birnbaumer, L. (1983) Stimulation and inhibition of adenylyl cyclases mediated by distinct regulatory proteins. *Nature* 302: 706-709.

Iyengar, R. and Herberg, J.T. (1984) Structural analysis of the hepatic glucagon receptor: identification of a guanine nucleotide-sensitive hormone binding region. *J. Biol. Chem.* 259: 522-529.

Codina, J., Hildebrandt, J.D., Sekura, R.D., Birnbaumer, M. Bryan, J., Manclark, R., Iyengar, R., and Birnbaumer, L. (1984) N_s and N_i : the stimulatory and inhibitory regulatory components of adenylyl cyclases. Purification of the human erythrocyte proteins without the use of activating regulatory ligands. *J. Biol. Chem.* 259: 5871-5866.

Rich, K.A., Codina, J., Floyd, G., Sekura, R., Hildebrandt, J.D. and Iyengar, R. (1984) Glucagon-induced heterologous desensitization of the MDCK cell adenylyl cyclase: increases in the apparent levels of the inhibitory regulatory (N_i). *J. Biol. Chem.* 259: 7893-7901.

Iyengar, R. and Herberg, J.T. (1985) Wheat germ lectin-sepharose affinity absorption assay for the glucagon receptor. *Meth. Enzymol.* 109: 13-19.

Iyengar, R. and Birnbaumer, L. (1987) Signal transduction by G-proteins. *ISI Atlas of Science* 1: 213-221.

Iyengar, R., Rich, K.A., Herberg, J.T., Premont, R.T. and Codina, J. (1988) Glucagon receptor mediated activation of G_s is accompanied by subunit dissociation. *J. Biol. Chem.* 263: 15348-15353.

Moriarty, T., Gillo, B., Carty, D.J., Premont, R.T., Landau, E.M. and Iyengar, R. (1988) The $\beta\gamma$ -subunits of G proteins inhibit muscarinic stimulation of IP₃ mediated chloride current. *Proc. Natl. Acad. Sci. USA* 85: 8865-8869.

Yatani, Y., Mattera, R., Codina, J., Graf, R., Okabe, K., Padrell, E., Iyengar, R., Brown, A.M., and Birnbaumer, L. (1988) The G-protein gated atrial K^+ channel is stimulated by three distinct G_i - α subunits. *Nature* 343: 680-682.

Premont, R.T., Buku, A., and Iyengar, R. (1989) The G_z - α gene product in human erythrocytes: identification as a 41 kDa protein. *J. Biol. Chem.* 264: 14960-14964.

Moriarty, T., Padrell, E., Carty, D.J., Omri, G., Landau, E.M. and Iyengar, R. (1990) The G-protein G_o can serve as the signal transducer in the pertussis-toxin sensitive phosphatidyl inositol pathway in *Xenopus* oocytes. *Nature* 343: 79-82.

Carty, D.J., Padrell, E., Codina, J., Birnbaumer, L., Hildebrandt, J.D., and Iyengar, R. (1990) Distinct guanine nucleotide binding and release properties of the three G_i proteins. *J. Biol. Chem.* 265: 6268-6273.

Iyengar, R. and Birnbaumer, L. (1990) An overview in *G Proteins*. R. Iyengar and L. Birnbaumer, eds., Academic Press, pp. 1-17.

Carty, D., Premont, R.T. and Iyengar, R. (1991) Quantitative immunoblotting of G-protein subunits. *Meth. Enzymol.* 195: 302-315.

Codina, J., Carty, D., Birnbaumer, L., and Iyengar, R. (1991) Purification of heterotrimeric G proteins. *Meth. Enzymol.* 195: 177-188.

Padrell, E., Carty, D.J., Moriarty, T.M., Hildebrandt, J.D., Landau, E.M., and Iyengar, R. (1991) Two forms of the bovine brain G_o that stimulate the IP₃ mediated Cl^- currents in *Xenopus* oocytes: distinct guanine nucleotide binding proteins. *J. Biol. Chem.* 266: 9771-9777.

- Kroll, S.D., Omri, G., Landau, E.M. and Iyengar, R. (1991) Activated $G_{O-\alpha}$ protein induces oocyte maturation. *Proc. Natl. Acad. Sci. USA* 88: 5182-5186.
- Premont, R.T., Chen, M., Ma, H.W., Ponnappalli, M. and Iyengar, R. (1992) Two members of a new subfamily of hormone stimulated adenylyl cyclases. *Proc. Natl. Acad. Sci. USA* 89: 9808-9813.
- De Vivo, M., Chen, J., Codina, J., and Iyengar, R. (1992) Enhanced stimulation of phospholipase C activity and cell transformation in NIH-3T3 cells expressing active Q209L Gq- α subunits. *J. Biol. Chem.* 267: 18263-18266.
- Kroll, S.D., Chen, J., De Vivo, M., Carty, D.J., Buku, A., Premont, R.T., and Iyengar, R. (1992) The Q205- α_o subunit expressed in NIH-3T3 cells induces transformation. *J. Biol. Chem.* 267: 23181-23188.
- Premont, R.T., Jacobowitz, O., and Iyengar, R. (1992) Lowered responsiveness of the catalyst of adenylyl cyclase to stimulation by G_s in heterologous desensitization: a role for cAMP-dependent phosphorylation. *Endocrinology* 131: 2774-2784.
- Jacobowitz, O., Chen, J., Premont, R.T., and Iyengar, R. (1993) Stimulation of specific types of G_s stimulated adenylyl cyclases by phorbol ester treatment. *J. Biol. Chem.* 268: 3829-3832.
- Blitzer, R.D., Omri, G., De Vivo, M.D., Carty, D.J., Premont, R.T., Codina, J., Birnbaumer, L., Cottechia, S., Caron, M.G., Lefkowitz, R.J., Landau, E.M., and Iyengar, R. (1993) Coupling of the expressed α_{1B} -adrenergic receptor to phospholipase C pathway in *Xenopus* oocytes. The role of G_o . *J. Biol. Chem.* 268: 12253-12256.
- Chen, J.Q. and Iyengar, R. (1993) Inhibition of cloned adenylyl cyclases by mutant activated $G_i-\alpha$ and specific suppression of type 2 adenylyl cyclase inhibition by phorbol ester treatment. *J. Biol. Chem.* 268: 12253-12256.
- Ma, H.W., Blitzer, R.D., Healy, E.C., Premont, R.T., Landau, E.M. Iyengar, R. (1993) Receptor evoked Cl^- current in *Xenopus* oocytes is mediated through a β -type phospholipase C: Cloning of a new form of the enzyme. *J. Biol. Chem.* 268: 19915-19918.
- Iyengar, R. (1993) Molecular and functional diversity of mammalian G_s stimulated adenylyl cyclases. *FASEB J.* 7: 768-775.
- Chen, J.H. and Iyengar, R. (1994) Suppression of Ras-induced transformation of NIH-3T3 cells by activated G_{α_s} . *Science* 263: 1278-1281.
- Jacobowitz, O. and Iyengar, R. (1994) Phorbol ester-induced stimulation and phosphorylation of adenylyl cyclase 2. *Proc. Natl. Acad. Sci. USA* 91: 10630-10634.
- De Vivo, M. and Iyengar, R. (1994) Activated Gq- α potentiates PDGF-stimulated mitogenesis in confluent cell cultures. *J. Biol. Chem.* 269: 19671-19674.
- Chen, J.Q., De Vivo, M., Dingus, J., Harry, A., Li, J.K., Sui, J., Carty, D.J., Blank, J.L., Exton, J., Stoffel, R.H., Inglese, J., Lefkowitz, R.J., Logothetis, D.E., Hildebrandt, J.D. and Iyengar, R. (1995) A region of adenylyl cyclase 2 is critical for regulation by G protein $\beta\gamma$ subunits. *Science* 268: 1166-1169.
- Mons, N., Harry, A., Duborg, P., Premont, R.T., Iyengar, R. and Cooper, D.M.F. (1995) Immunohistochemical localization of adenylyl cyclase in rat brain indicates a highly selective concentration at synapses. *Proc. Natl. Acad. Sci. USA* 92: in press.
- Pieroni, J.P., Harry, A., Chen, J.Q., Jacobowitz, O., Magnusson, R.P. and Iyengar, R. (1995) Distinct characteristics of the basal activities of adenylyl cyclase 2 and 6. *J. Biol. Chem.* 270: in press.

TRAINING RECORD - PREDOCTORAL STUDENTS AND POSTDOCTORAL FELLOWS

FACULTY MEMBER: Ravi Iyengar, Ph.D.

Present Predoctoral Students:

Name	Prior Education			Training		
	Degree(s)	Yr(s)	Institution(s)	Period	Department or Subarea	Source of support
Chen, J.-Q.	B.S.	1986	Shanghai Med. College	1992-	Pharmacology	NIH CA 44998
Harry, A.	B.A.	1988	New York Univ.	1992-	Pharmacology	MARC fellowship
Santore, T.A.	B.S. M.S.	1990 1992	St. Francis College Long Island Univ.	1994-	Biochemistry	ACS CD 518
Holness, W.	B.S.	1993	Medgar Evers Coll.	1994-	Molecular Biology	NIH DK 38761
Crowder, S.	B.S.	1993	U.C.-Santa Barbara	1994-	Pharmacology	Grad. School funds

Past Predoctoral Students:

Name	Prior Education			Training			Current Position
	Degree(s)	Yr(s)	Institution(s)	Period	Degree obtained	Department or Subarea	
Padrell, E.				1985-1990	Ph.D.	Pharmacology	Resident, Psychiatry, Mount Sinai
Moriarty, T.M.	B.S.	1983	SUNY-Buffalo	1987-1990	Ph.D.	Pharmacology	Resident, Neurosurgery, Mass. General Hospital
Kroll, S.D.	B.S.	1988	Cornell	1988-91	Ph.D.	Pharmacology	Med. Student, Georgetown Med. School
Premont, R.T.	B.S.	1985	Caltech	1987-91	Ph.D.	Pharmacology	Postdoctoral Fellow, Duke Medical Center

TRAINING RECORD - PREDOCTORAL STUDENTS AND POSTDOCTORAL FELLOWS

Chen, J.-H.	B.S.	1985	U. Science & Technol., Hefei, P.R.C.	1990-94	Ph.D.	Biochemistry	Postdoctoral Associate, Mount Sinai
Jacobowitz, O.	B.S.	1989	MIT	1990-95	Ph.D.	Pharmacology	Med. student, Mount Sinai School of Medicine
Ma, H.-W.	B.M.	1991	Shanghai Med. College	1990-95	Ph.D.	Molecular Biol.	Med. student, Shanghai Med. College, P.R.C.

Faculty Member: R. Iyengar

Present Postdoctoral Fellows:

Name	Prior Education			Training		
	Degree(s)	Yr(s)	Institution(s)	Period	Department	Source of support
DeVivo, M.	Ph.D.	1987	MSSM	1990-	Pharmacology	Aaron Diamond Fellow
Pieroni, J.	Ph.D.	1988	New York Med. College	1992	Pharmacology	CA 44998
Bhalla, U.	Ph.D.	1993	Caltech	1993-	Pharmacology	DK 38761

Past Postdoctoral Fellows:

Name	Prior Education			Training		
	Degree(s)	Yr(s)	Institution(s)	Period	Department	Current Position
Rich, K.J.	Ph.D.	1980	Monash Univ., Australia	1982-85		Assist. Professor, USC Med. Schl.
Chung H.S.	Ph.D.	1987	CUNY	1987-88		Assist. Professor, Kyung-Hee Univ., Korea
Carty, D.J.	Ph.D.	1981	U. Virginia	1987-90		Res. Assistant Profceesor, Mount Sinai Schl. Med.

THE MOUNT SINAI MEDICAL CENTER
THE MOUNT SINAI HOSPITAL * MOUNT SINAI SCHOOL OF MEDICINE
MOUNT SINAI CANCER CENTER BREAST STUDY GROUP
ONE GUSTAVE L. LEVY PLACE * BOX 1130
NEW YORK, NEW YORK 10029

FROM: Dr. Stuart Aaronson
Dr. Steven T. Brower

DATE: November 10, 1994

TO: Breast Cancer Study
Group/MSMC

The next scheduled meeting for the Mount Sinai Cancer Center Breast Study Group will be held on December 15, 1994 at 12:00 Noon in Conference C - GP Building-2nd Floor.

Dr. Edward Johnson will be the invited speaker for this event. The topic for the lecture will be announced through the Weekly Medical Bulletin.

Any questions, please feel free to contact Mr. John Buzos at ext. 46470 or Mr. Angel Garcia at ext. 48026.

LUNCHEON WILL BE SERVED

Thank you.

MOUNT SINAI CANCER CENTER BREAST STUDY GROUP
One Gustave L. Levy Place, Box # 1130
New York, NY 10029

M E M O R A N D U M

FROM: **Stuart Aaronson, M.D.**
 Director
 Derald Ruttenberg Cancer Center

Steven T. Brower, M.D.
 Chief
 Division of Surgical Oncology

TO: ***Distribution/Cancer Center Study Group***

The next Cancer Center Breast Study Group meeting will be held at 12:00 P.M. on July 27, 1995 in Conference Room Annenberg 25-51.

A G E N D A

- 1. New Breast Cancer Funding Opportunities**
 Dr. Stuart Aaronson
 Director, Derald Ruttenberg Cancer Center
- 2. Student Research Projects for the Cancer Center Breast Study Group.**
 Max Fonarov-Student/J. Manfredi, MD-Preceptor
 Ullrich Hermanto-Student/L. Wang, MD-Preceptor
 Tara Santore-Student/Ravi Iyengar, MD-Preceptor

Should you have any questions, please feel free to call Mr. Angel Garcia at ext. 48026 or Mr. John Bazos at ext. 46470.

Thank you.

L U N C H W I L L B E S E R V E D